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<110> MAURER, MARTIN
FELDMANN, ROBERT E.
KUSCHINSKY, WOLFGANG
SCHNEIDER, ARMIN

<120> A PROCESS FOR IN VITRO DIFFERENTIATION OF NEURAL STEM CELLS OR OF CELLS DERIVED FROM NEURONAL STEM CELLS

<130> 085449-0198

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<141> 2008-10-15

<150> PCT/EP04/014673
<151> 2004-12-23

<150> DE 10361444.3
<151> 2003-12-23

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<170> PatentIn Ver. 3.3

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<213> Homo sapiens

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Asp Arg Lys Ala Ala Val Ser His Trp Gln Gln Gln Ser Tyr Leu Asp
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Ser Gly Ile His Ser Gly Ala Thr Thr Thr Ala Pro Ser Leu Ser Gly
         35                  40                  45

Lys Gly Asn Pro Glu Glu Glu Asp Val Asp Thr Ser Gln Val Leu Tyr
     50                  55                  60

Glu Trp Glu Gln Gly Phe Ser Gln Ser Phe Thr Gln Glu Gln Val Ala
 65                  70                  75                  80

Asp Ile Asp Gly Gln Tyr Ala Met Thr Arg Ala Gln Arg Val Arg Ala
                 85                  90                  95

Ala Met Phe Pro Glu Thr Leu Asp Glu Gly Met Gln Ile Pro Ser Thr
            100                 105                 110

Gln Phe Asp Ala Ala His Pro Thr Asn Val Gln Arg Leu Ala Glu Pro
        115                 120                 125

Ser Gln Met Leu Lys His Ala Val Val Asn Leu Ile Asn Tyr Gln Asp
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    130                 135                 140

Asp Ala Glu Leu Ala Thr Arg Ala Ile Pro Glu Leu Thr Lys Leu Leu
145                 150                 155                 160

Asn Asp Glu Asp Gln Val Val Val Asn Lys Ala Ala Val Met Val His
                165                 170                 175

Gln Leu Ser Lys Lys Glu Ala Ser Arg His Ala Ile Met Arg Ser Pro
            180                 185                 190

Gln Met Val Ser Ala Ile Val Arg Thr Met Gln Asn Thr Asn Asp Val
        195                 200                 205

Glu Thr Ala Arg Cys Thr Ala Gly Thr Leu His Asn Leu Ser His His
    210                 215                 220

Arg Glu Gly Leu Leu Ala Ile Phe Lys Ser Gly Gly Ile Pro Ala Leu
225                 230                 235                 240

Val Lys Met Leu Gly Ser Pro Val Asp Ser Val Leu Phe Tyr Ala Ile
                245                 250                 255

Thr Thr Leu His Asn Leu Leu Leu His Gln Glu Gly Ala Lys Met Ala
            260                 265                 270

Val Arg Leu Ala Gly Gly Leu Gln Lys Met Val Ala Leu Leu Asn Lys
        275                 280                 285

Thr Asn Val Lys Phe Leu Ala Ile Thr Thr Asp Cys Leu Gln Ile Leu
    290                 295                 300

Ala Tyr Gly Asn Gln Glu Ser Lys Leu Ile Ile Leu Ala Ser Gly Gly
305                 310                 315                 320

Pro Gln Ala Leu Val Asn Ile Met Arg Thr Tyr Thr Tyr Glu Lys Leu
                325                 330                 335

Leu Trp Thr Thr Ser Arg Val Leu Lys Val Leu Ser Val Cys Ser Ser
            340                 345                 350

Asn Lys Pro Ala Ile Val Glu Ala Gly Gly Met Gln Ala Leu Gly Leu
        355                 360                 365

His Leu Thr Asp Pro Ser Gln Arg Leu Val Gln Asn Cys Leu Trp Thr
    370                 375                 380

Leu Arg Asn Leu Ser Asp Ala Ala Thr Lys Gln Glu Gly Met Glu Gly
385                 390                 395                 400

Leu Leu Gly Thr Leu Val Gln Leu Leu Gly Ser Asp Asp Ile Asn Val
                405                 410                 415

Val Thr Cys Ala Ala Gly Ile Leu Ser Asn Leu Thr Cys Asn Asn Tyr
            420                 425                 430

Lys Asn Lys Met Met Val Cys Gln Val Gly Gly Ile Glu Ala Leu Val
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        435                 440                 445

Arg Thr Val Leu Arg Ala Gly Asp Arg Glu Asp Ile Thr Glu Pro Ala
    450                 455                 460

Ile Cys Ala Leu Arg His Leu Thr Ser Arg His Gln Glu Ala Glu Met
465                 470                 475                 480

Ala Gln Asn Ala Val Arg Leu His Tyr Gly Leu Pro Val Val Val Lys
                485                 490                 495

Leu Leu His Pro Pro Ser His Trp Pro Leu Ile Lys Ala Thr Val Gly
            500                 505                 510

Leu Ile Arg Asn Leu Ala Leu Cys Pro Ala Asn His Ala Pro Leu Arg
        515                 520                 525

Glu Gln Gly Ala Ile Pro Arg Leu Val Gln Leu Leu Val Arg Ala His
    530                 535                 540

Gln Asp Thr Gln Arg Arg Thr Ser Met Gly Gly Thr Gln Gln Gln Phe
545                 550                 555                 560

Val Glu Gly Val Arg Met Glu Glu Ile Val Glu Gly Cys Thr Gly Ala
                565                 570                 575

Leu His Ile Leu Ala Arg Asp Val His Asn Arg Ile Val Ile Arg Gly
            580                 585                 590

Leu Asn Thr Ile Pro Leu Phe Val Gln Leu Leu Tyr Ser Pro Ile Glu
        595                 600                 605

Asn Ile Gln Arg Val Ala Ala Gly Val Leu Cys Glu Leu Ala Gln Asp
    610                 615                 620

Lys Glu Ala Ala Glu Ala Ile Glu Ala Glu Gly Ala Thr Ala Pro Leu
625                 630                 635                 640

Thr Glu Leu Leu His Ser Arg Asn Glu Gly Val Ala Thr Tyr Ala Ala
                645                 650                 655

Ala Val Leu Phe Arg Met Ser Glu Asp Lys Pro Gln Asp Tyr Lys Lys
            660                 665                 670

Arg Leu Ser Val Glu Leu Thr Ser Ser Leu Phe Arg Thr Glu Pro Met
        675                 680                 685

Ala Trp Asn Glu Thr Ala Asp Leu Gly Leu Asp Ile Gly Ala Gln Gly
    690                 695                 700

Glu Pro Leu Gly Tyr Arg Gln Asp Asp Pro Ser Tyr Arg Ser Phe His
705                 710                 715                 720

Ser Gly Gly Tyr Gly Gln Asp Ala Leu Gly Met Asp Pro Met Met Glu
                725                 730                 735

His Glu Met Gly Gly His His Pro Gly Ala Asp Tyr Pro Val Asp Gly
```

```
            740                 745                 750

Leu Pro Asp Leu Gly His Ala Gln Asp Leu Met Asp Gly Leu Pro Pro
        755                 760                 765

Gly Asp Ser Asn Gln Leu Ala Trp Phe Asp Thr Asp Leu
    770                 775                 780
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<213> Homo sapiens

<400> 2

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Val Gln Gln Pro Ser Ala Phe Gly Ser Met Lys Val Ser Arg Asp Lys
             20                  25                  30

Asp Gly Ser Lys Val Thr Thr Val Val Ala Thr Pro Gly Gln Gly Pro
         35                  40                  45

Asp Arg Pro Gln Glu Val Ser Tyr Thr Asp Thr Lys Val Ile Gly Asn
     50                  55                  60

Gly Ser Phe Gly Val Val Tyr Gln Ala Lys Leu Cys Asp Ser Gly Glu
 65                  70                  75                  80

Leu Val Ala Ile Lys Lys Val Leu Gln Asp Lys Arg Phe Lys Asn Arg
                 85                  90                  95

Glu Leu Gln Ile Met Arg Lys Leu Asp His Cys Asn Ile Val Arg Leu
            100                 105                 110

Arg Tyr Phe Phe Tyr Ser Ser Gly Glu Lys Lys Asp Glu Val Tyr Leu
        115                 120                 125

Asn Leu Val Leu Asp Tyr Val Pro Glu Thr Val Tyr Arg Val Ala Arg
    130                 135                 140

His Tyr Ser Arg Ala Lys Gln Thr Leu Pro Val Ile Tyr Val Lys Leu
145                 150                 155                 160

Tyr Met Tyr Gln Leu Phe Arg Ser Leu Ala Tyr Ile His Ser Phe Gly
                165                 170                 175

Ile Cys His Arg Asp Ile Lys Pro Gln Asn Leu Leu Leu Asp Pro Asp
            180                 185                 190

Thr Ala Val Leu Lys Leu Cys Asp Phe Gly Ser Ala Lys Gln Leu Val
        195                 200                 205

Arg Gly Glu Pro Asn Val Ser Tyr Ile Cys Ser Arg Tyr Tyr Arg Ala
    210                 215                 220
```

```
Pro Glu Leu Ile Phe Gly Ala Thr Asp Tyr Thr Ser Ser Ile Asp Val
225                 230                 235                 240

Trp Ser Ala Gly Cys Val Leu Ala Glu Leu Leu Leu Gly Gln Pro Ile
                245                 250                 255

Phe Pro Gly Asp Ser Gly Val Asp Gln Leu Val Glu Ile Ile Lys Val
            260                 265                 270

Leu Gly Thr Pro Thr Arg Glu Gln Ile Arg Glu Met Asn Pro Asn Tyr
        275                 280                 285

Thr Glu Phe Lys Phe Pro Gln Ile Lys Ala His Pro Trp Thr Lys Val
    290                 295                 300

Phe Arg Pro Arg Thr Pro Pro Glu Ala Ile Ala Leu Cys Ser Arg Leu
305                 310                 315                 320

Leu Glu Tyr Thr Pro Thr Ala Arg Leu Thr Pro Leu Glu Ala Cys Ala
                325                 330                 335

His Ser Phe Phe Asp Glu Leu Arg Asp Pro Asn Val Lys Leu Pro Asn
            340                 345                 350

Gly Arg Asp Thr Pro Ala Leu Phe Asn Phe Thr Thr Gln Glu Leu Ser
        355                 360                 365

Ser Asn Pro Pro Leu Ala Thr Ile Leu Ile Pro Pro His Ala Arg Ile
    370                 375                 380

Gln Ala Ala Ala Ser Thr Pro Thr Asn Ala Thr Ala Ala Ser Asp Ala
385                 390                 395                 400

Asn Thr Gly Asp Arg Gly Gln Thr Asn Asn Ala Ala Ser Ala Ser Ala
                405                 410                 415

Ser Asn Ser Thr
            420


<210> 3
<211> 648
<212> PRT
<213> Homo sapiens

<400> 3
Met Ala Glu Glu Glu Ala Pro Lys Lys Ser Arg Ala Ala Gly Gly Gly
  1               5                  10                  15

Ala Ser Trp Glu Leu Cys Ala Gly Ala Leu Ser Ala Arg Leu Ala Glu
             20                  25                  30

Glu Gly Ser Gly Asp Ala Gly Gly Arg Arg Arg Pro Pro Val Asp Pro
         35                  40                  45

Arg Arg Leu Ala Arg Gln Leu Leu Leu Leu Leu Trp Leu Leu Glu Ala
     50                  55                  60
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```
Pro Leu Leu Leu Gly Val Arg Ala Gln Ala Ala Gly Gln Gly Pro Gly
 65                  70                  75                  80

Gln Gly Pro Gly Pro Gly Gln Gln Pro Pro Pro Pro Pro Pro Gln Gln
                 85                  90                  95

Gln Gln Ser Gly Gln Gln Tyr Asn Gly Glu Arg Gly Ile Ser Val Pro
            100                 105                 110

Asp His Gly Tyr Cys Gln Pro Ile Ser Ile Pro Leu Cys Thr Asp Ile
        115                 120                 125

Ala Tyr Asn Gln Thr Ile Met Pro Asn Leu Leu Gly His Thr Asn Gln
    130                 135                 140

Glu Asp Ala Gly Leu Glu Val His Gln Phe Tyr Pro Leu Val Lys Val
145                 150                 155                 160

Gln Cys Ser Ala Glu Leu Lys Phe Phe Leu Cys Ser Met Tyr Ala Pro
                165                 170                 175

Val Cys Thr Val Leu Glu Gln Ala Leu Pro Pro Cys Arg Ser Leu Cys
            180                 185                 190

Glu Arg Ala Arg Gln Gly Cys Glu Ala Leu Met Asn Lys Phe Gly Phe
        195                 200                 205

Gln Trp Pro Asp Thr Leu Lys Cys Glu Lys Phe Pro Val His Gly Ala
    210                 215                 220

Gly Glu Leu Cys Val Gly Gln Asn Thr Ser Asp Lys Gly Thr Pro Thr
225                 230                 235                 240

Pro Ser Leu Leu Pro Glu Phe Trp Thr Ser Asn Pro Gln His Gly Gly
                245                 250                 255

Gly Gly His Arg Gly Gly Phe Pro Gly Gly Ala Gly Ala Ser Glu Arg
            260                 265                 270

Gly Lys Phe Ser Cys Pro Arg Ala Leu Lys Val Pro Ser Tyr Leu Asn
        275                 280                 285

Tyr His Phe Leu Gly Glu Lys Asp Cys Gly Ala Pro Cys Glu Pro Thr
    290                 295                 300

Lys Val Tyr Gly Leu Met Tyr Phe Gly Pro Glu Glu Leu Arg Phe Ser
305                 310                 315                 320

Arg Thr Trp Ile Gly Ile Trp Ser Val Leu Cys Cys Ala Ser Thr Leu
                325                 330                 335

Phe Thr Val Leu Thr Tyr Leu Val Asp Met Arg Arg Phe Ser Tyr Pro
            340                 345                 350

Glu Arg Pro Ile Ile Phe Leu Ser Gly Cys Tyr Thr Ala Val Ala Val
        355                 360                 365
```

```
Ala Tyr Ile Ala Gly Phe Leu Leu Glu Asp Arg Val Val Cys Asn Asp
    370                 375                 380

Lys Phe Ala Glu Asp Gly Ala Arg Thr Val Ala Gln Gly Thr Lys Lys
385                 390                 395                 400

Glu Gly Cys Thr Ile Leu Phe Met Met Leu Tyr Phe Phe Ser Met Ala
                405                 410                 415

Ser Ser Ile Trp Trp Val Ile Leu Ser Leu Thr Trp Phe Leu Ala Ala
            420                 425                 430

Gly Met Lys Trp Gly His Glu Ala Ile Glu Ala Asn Ser Gln Tyr Phe
        435                 440                 445

His Leu Ala Ala Trp Ala Val Pro Ala Ile Lys Thr Ile Thr Ile Leu
    450                 455                 460

Ala Leu Gly Gln Val Asp Gly Asp Val Leu Ser Gly Val Cys Phe Val
465                 470                 475                 480

Gly Leu Asn Asn Val Asp Ala Leu Arg Gly Phe Val Leu Ala Pro Leu
                485                 490                 495

Phe Val Tyr Leu Phe Ile Gly Thr Ser Phe Leu Leu Ala Gly Phe Val
            500                 505                 510

Ser Leu Phe Arg Ile Arg Thr Ile Met Lys His Asp Gly Thr Lys Thr
        515                 520                 525

Glu Lys Leu Glu Lys Leu Met Val Arg Ile Gly Val Phe Ser Val Leu
    530                 535                 540

Tyr Thr Val Pro Ala Thr Ile Val Ile Ala Cys Tyr Phe Tyr Glu Gln
545                 550                 555                 560

Ala Phe Arg Asp Gln Trp Glu Arg Ser Trp Val Ala Gln Ser Cys Lys
                565                 570                 575

Ser Tyr Ala Ile Pro Cys Pro His Leu Gln Ala Gly Gly Gly Ala Pro
            580                 585                 590

Pro His Pro Pro Met Ser Pro Asp Phe Thr Val Phe Met Ile Lys Tyr
        595                 600                 605

Leu Met Thr Leu Ile Val Gly Ile Thr Ser Gly Phe Trp Ile Trp Ser
    610                 615                 620

Gly Lys Thr Leu Asn Ser Trp Arg Lys Phe Tyr Thr Arg Leu Thr Asn
625                 630                 635                 640

Ser Lys Gln Gly Glu Thr Thr Val
                645
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<210> 4

<211> 565
<212> PRT
<213> Homo sapiens

<400> 4
Met Arg Pro Arg Ser Ala Leu Pro Arg Leu Leu Leu Pro Leu Leu Leu
  1   5   10   15

Leu Pro Ala Ala Gly Pro Ala Gln Phe His Gly Glu Lys Gly Ile Ser
             20   25   30

Ile Pro Asp His Gly Phe Cys Gln Pro Ile Ser Ile Pro Leu Cys Thr
         35   40   45

Asp Ile Ala Tyr Asn Gln Thr Ile Met Pro Asn Leu Leu Gly His Thr
     50   55   60

Asn Gln Glu Asp Ala Gly Leu Glu Val His Gln Phe Tyr Pro Leu Val
 65   70   75   80

Lys Val Gln Cys Ser Pro Glu Leu Arg Phe Phe Leu Cys Ser Met Tyr
                 85   90   95

Ala Pro Val Cys Thr Val Leu Glu Gln Ala Ile Pro Pro Cys Arg Ser
            100   105   110

Ile Cys Glu Arg Ala Arg Gln Gly Cys Glu Ala Leu Met Asn Lys Phe
        115   120   125

Gly Phe Gln Trp Pro Glu Arg Leu Arg Cys Glu His Phe Pro Arg His
    130   135   140

Gly Ala Glu Gln Ile Cys Val Gly Gln Asn His Ser Glu Asp Gly Ala
145   150   155   160

Pro Ala Leu Leu Thr Thr Ala Pro Pro Pro Gly Leu Gln Pro Gly Ala
                165   170   175

Gly Gly Thr Pro Gly Gly Pro Gly Gly Gly Gly Ala Pro Pro Arg Tyr
            180